

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**TUMOUR NECROSIS FACTOR BINDING LIGANDS**

the specification of which (check only one item below):

☐ is attached hereto.

☒ was filed as United States application

Serial No. 08/344,133

on November 23, 1994

and was amended

on \_\_\_\_\_ (if applicable).

☐ was filed as PCT international application

Number \_\_\_\_\_

on \_\_\_\_\_

and was amended under PCT Article 19

on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

**PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:**

COUNTRY (If PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 USC 119
AUSTRALIA	PJ5662	7 August 1989	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
AUSTRALIA	PJ7576	24 November 1989	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
PCT	PCT/AU90/00337	7 August 1990	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO
			<input type="checkbox"/> YES <input type="checkbox"/> NO

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

**PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:**

U.S. APPLICATIONS		STATUS (Check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
07/828,956	February 18, 1992		X	
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED (If any)		

**POWER OF ATTORNEY:** As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (List name and registration number)

(See Attached Power of Attorney)

**Send Correspondence to:**

John J. McDonnell, Esq.  
ALLEGRETTI & WITCOFF, LTD.  
10 South Wacker Drive - Suite 3000  
Chicago, Illinois 60606

**Direct Telephone Calls to:**  
(name and telephone number)

John J. McDonnell  
(312) 715-1000

201	FULL NAME OF INVENTOR	FAMILY NAME RATHJEN	FIRST GIVEN NAME DEBORAH	SECOND GIVEN NAME ANN
	RESIDENCE & CITIZENSHIP	CITY New South Wales	STATE OR FOREIGN COUNTRY Australia	COUNTRY OF CITIZENSHIP Australia
	POST OFFICE ADDRESS	POST OFFICE ADDRESS 4 Eddy Street	CITY Thornleigh	STATE & ZIP CODE/COUNTRY NSW 2099 AUSTRALIA
202	FULL NAME OF INVENTOR	FAMILY NAME ASTON	FIRST GIVEN NAME ROGER	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY Gloucester	STATE OR FOREIGN COUNTRY Great Britain	COUNTRY OF CITIZENSHIP Great Britain
	POST OFFICE ADDRESS	POST OFFICE ADDRESS The Barnhouse, Ham Lane	CITY South Cerney Cirencester	STATE & ZIP CODE/COUNTRY Gloucester GL7 5UF / Great Britain
203	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201

X *Deborah Rathjen*

SIGNATURE OF INVENTOR 202

X *Roger Aston*

SIGNATURE OF INVENTOR 203

DATE

X 20<sup>th</sup> February 1995

DATE

8<sup>th</sup> February 1995

DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Deborah A. RATHJEN and Roger  
ASTON

Serial No.: 09/736,792

Filing Date: December 13, 2000

For: TUMOR NECROSIS FACTOR  
BINDING LIGANDS

Examiner: J. Roark

Group Art Unit: 1644

DECLARATION OF JOHN YOUNG YUEN  
PURSUANT TO 37 C.F.R § 1.132

Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

I, John Young Yuen, declare as follows:

1. I am an employee of Peptech Ltd, Unit 1, 35-41 Waterloo Road, North Ryde, NSW 2113 Australia. I have been employed at Peptech Ltd. since 1986 as a Research Officer.
2. I currently reside at 26 Albert Road Auburn NSW 2144 Australia.
3. I am familiar with the contents of the above-referenced patent application, and U.S. Pat. App. Ser. Nos. 09/737,121, 09/736,630 and 09/736,793. The four above-referenced patent applications were filed on December 13, 2000 and are each a continuation of U.S. Pat. App. Ser. No. 09/364,039, thereby having identical specifications.
4. In October 1989 I was requested by Deborah A. Rathjen to synthesize the peptides referred to as peptides 309 (page 32, lines 3-5) and 323 (page 32, lines 6-7) in the above-referenced patent applications and in Exhibits 1 and 2, attached hereto in the Appendix. These peptides correspond to residues 73-94 (peptide 309) and residues 79-89 (peptide 323) of mature human TNF- $\alpha$ .

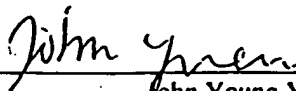
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5. The peptides were synthesized according to the techniques described on pages 30-33 of the specification of application Serial No. 09/364,039, according to the sequences disclosed in Exhibit 1 and 2 (Appendix), which are identical to the sequences for the corresponding regions as disclosed in Pennica *et al.* (1984) *Nature* 312:724-729 "Human tumor necrosis factor: precursor structure, expression and homology to lymphotoxin" (submitted in the 09/364,039 application with the May 25, 2001 Declaration pursuant to 37 C.F.R § 1.132 of Deborah A. Rathjen, the entirety of which is incorporated herein by reference). These regions of sequence are in agreement with other sequences published for hTNF-  $\alpha$  and accepted by those of skill in the art to be the correct sequence of hTNF- $\alpha$ .

6. In Pennica *et al.*, residue 87 is shown as the amino acid Tyr (page 725, Figure 1; page 728, Figure 4), in agreement with other published sequences, such as those available in public databases, copies of which were submitted with the May 25, 2001 Declaration pursuant to 37 C.F.R § 1.132 of Deborah A. Rathjen. It would be obvious to one of ordinary skill in the art that the Tyr->Thr switches in peptides 309 and 323 at position 87 listed in application Serial No. 09/364,039 are typographical errors when viewed in the context of Pennica *et al.* and other publicly available sequences which list amino acid 87 as Tyr-87. It would also be obvious to one of skill in the art that the correction of the sequences in the specification of the above-referenced applications would entail replacing Thr with Tyr at position 87 in peptides 309 and 323.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

18 April 2002  
Date

  
\_\_\_\_\_  
John Young Yuen

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Deborah A. RATHJEN and Roger  
ASTON

Serial No.: 09/737,121

Filing Date: December 13, 2000

For: TUMOR NECROSIS FACTOR  
BINDING LIGANDS

Examiner: J. Roark

Group Art Unit: 1644

DECLARATION OF STEPHEN KWIK  
PURSUANT TO 37 C.F.R § 1.132

Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

I, STEPHEN KWIK, declare as follows:

1. I am Managing Director of Peptech Limited, the assignee of the above-referenced patent application and U.S. Pat. App. Ser. Nos. 09/736,792 and 09/364,039, and am familiar with the contents thereof. The three above-listed patent applications were filed on December 13, 2000 with inventors Deborah A. RATHJEN and Roger ASTON.

2. I currently reside at 20 Willowie Road, Castle Cove, NSW 2069, Australia.

3. Samples of the hybridoma cell lines listed below were deposited with the European Collection of Animal Cell Cultures (ECACC), Vaccine Research and Production Laboratory, Public Health Laboratory Service, Centre for Applied Microbiology and Research, Porton Down, Salisbury, Wiltshire SP4 0JG, United Kingdom on the dates indicated and accorded the accession numbers listed below:

a sample of the hybridoma producing MAb 1 was deposited on 3 August 1989 and accorded accession No. 89080301 (see application specification page 5 line 26-page 6, line 4);

a sample of the hybridoma producing MAb 54 was deposited on 31 August 1989 and accorded accession No. 89083103 (see application specification page 5 line 26-page 6, line 4);

a sample of the hybridoma producing MAb 47 was deposited on 14 December 1989 and accorded accession No. 89121402 (see application specification page 5 line 26-page 6, line 4);

a sample of the hybridoma producing MAb 32 was deposited on 3 August 1989 and was accorded accession No. 89080302 (see application specification page 7, lines 11-20);

a sample of the hybridoma cell line producing MAb 42 was deposited on 3 August 1989 and was accorded accession No. 89080304 (see application specification page 9, lines 20-29);

a sample of the hybridoma cell line producing MAb 21 was deposited on 25 January 1990 and was accorded accession No. 90012432 (see application specification page 11, line 29 through page 12, line 2);

a sample of the hybridoma cell line producing MAb 53 was deposited on 25 January 1990 and was accorded accession No. 90012433 (see application specification page 12, lines 29-36);

a sample of the hybridoma cell line producing MAb 37 was deposited on 3 August 1989 and was accorded accession No. 89080303 (see application specification page 13, lines 25-31).

4. I, on behalf of Applicants and their assign, hereby declare that upon granting of a patent from the above-referenced applications, all restrictions imposed by the depositor on the availability to the public of the above-referenced deposited material have been irrevocably removed, in accordance with U.S. 37 C.F.R. 1.808 a(2).

8-3-92

Date

  
STEPHEN KWIK, Managing Director

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Deborah A. RATHJEN and Roger  
ASTON

Serial No.: 09/364,039

Filing Date: July 30, 1999

For: TUMOR NECROSIS FACTOR  
BINDING LIGANDS

Examiner: J. Roark

Group Art Unit: 1644

DECLARATION OF DEBORAH A. RATHJEN  
PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents  
Washington, D.C. 20231

Dear Sir,

I, Deborah A. Rathjen, declare as follows:

1. I am an inventor of the above-referenced patent application, and am familiar with the contents thereof.
2. I currently reside at 86 Kingfisher Circuit, Flagstaff Hill, South Australia, Australia 5006.
3. I have reviewed the publication Socher *et al.* (1985) *Proc. Natl. Acad. Sci. USA* 84:8829-8833, cited in the specification of the above-listed application Serial No. 09/364,039 (page 3, lines 23-24) and submitted in the Supplemental IDS filed April 20, 2001. Except for the caveat described in paragraph 4, below, the cited publication lists the complete deduced sequence of mature recombinant human tumor necrosis factor  $\alpha$  (hTNF- $\alpha$ ) (page 8830, Figure 1A), which is a 157-residue protein of molecular weight approximately 17,000 kD.
4. As explained in my earlier Declaration pursuant to 37 C.F.R. § 1.132, submitted to the Office on May 25, 2001, and which is incorporated herein by reference, the hTNF- $\alpha$  amino

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acid sequence listed in Socher *et al.*, agrees with the amino acids listed in the peptide sequences in the application specification Serial No. 09/364,039 on page 31 (line 16) through page 32 (line 7) for all residues, with the exception of amino acid residues 59 and 87, verifying that the numbered peptide sequences in application Serial No. 09/364,039, and therefore the hTNF- $\alpha$  numbering used throughout the specification, correspond to the numbering of the mature hTNF- $\alpha$  protein.

5. The peptides synthesized as described on pages 30-33 of the specification of application Serial No. 09/364,039 were synthesized using the numbering system for mature hTNF- $\alpha$ , discussed in paragraph 4, above.

6. The amino acid sequences added by amendment of the specification, submitted herewith, correspond to regions of the amino acid sequence of hTNF- $\alpha$  as reported in Socher *et al.*, and are numbered according to the numbering convention used in Socher *et al.*

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

28/1/02

Date

  
Deborah A. RADEIEN



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the application of:

Deborah A. RATHJEN and Roger  
ASTON

Examiner: J. Roark

Group Art Unit: 1644

Serial No.: 09/364,039

Filing Date: July 30, 1999

For: TUMOR NECROSIS FACTOR  
BINDING LIGANDS

DECLARATION OF DEBORAH A. RATHJEN  
PURSUANT TO 37 C.F.R. § 1.132

Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

I, Deborah A. Rathjen, declare as follows:

1. I am an inventor of the above-referenced patent application, and am familiar with the contents thereof.
2. I currently reside at [INSERT]. *86 Kingfisher Circuit, Flagstaff Hill  
South Australia, Australia, 5006*
3. I have reviewed the publication Socher *et al.* (1985) *Proc. Natl. Acad. Sci. USA* 84:8829-8833, cited in the specification of the above-listed application Serial No. 09/364,039 and submitted in the Supplemental IDS filed April 20, 2001. The cited publication lists the complete deduced sequence of mature recombinant human tumor necrosis factor  $\alpha$  (hTNF- $\alpha$ ) (page 8830, Figure 1A), which is a 157-residue protein of molecular weight approximately 17,000 kD. The source (page 8832, column 1, 1st full paragraph) cited for this sequence is Pennica *et al.* (1984) *Nature* 312:724-729 "Human tumor necrosis factor: precursor structure, expression and homology to lymphotoxin" (Appendix) The primary amino acid sequence listed

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in Socher *et al.* is the mature form of the protein, as distinguished from the precursor protein which has an open reading frame of 233 amino acids in length (Pennica *et al.*).

4. The hTNF- $\alpha$  amino acid sequence listed in Socher *et al.*, agrees with the amino acids listed in the peptide sequences in the application specification Serial No. 09/364,039 on page 31 (line 16) through page 32 (line 7) for all residues, with the exception of amino acid residues 59 and 87, verifying that the numbered peptide sequences in application Serial No. 09/364,039, and therefore the hTNF- $\alpha$  numbering used throughout the specification, correspond to the numbering of the mature hTNF- $\alpha$  protein.

5. Regarding residues 59 and 87, Socher *et al.*, lists these residues as Thr-59 and Tyr-87, while application Serial No. 09/364,039 lists these residues as Tyr-59 and Thr-87. In Pennica *et al.*, both of these residues are shown as the amino acid Tyr (page 725, Figure 1; page 728, Figure 4). One of ordinary skill in the art would realize that the Tyr $\rightarrow$ Thr switches at position 59 in Socher *et al.*, and position 87 of application Serial No. 09/364,039 are typographical errors, as the earlier Pennica *et al.*, (cited in Socher *et al.*) is in agreement with sequences of the human TNF- $\alpha$  precursor (additional 76 residues at N-terminus) deposited in publicly accessible databases in, for example, 1985 (pir accession number QWHUN) and 1986 (SWISS-PROT accession number P01375) (see Appendix) and references cited therein.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

19 May 2001

(date)

Date

  
Deborah ALKATHIEN